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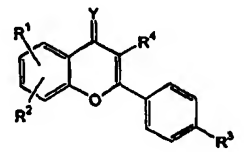

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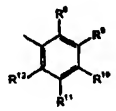

(a)

(b)

(c)

(d)

(57) Abstract

The diarylbenzopyran derivatives represented by general formula (I): wherein Y is an oxygen atom or a sulfur atom; R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1–C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group; R^3 is a group of a formula: $S(O)nR^5$ wherein n is an integer of 0~2, R^5 is a hydrogen atom, a C_1–C_6 lower alkyl group, or a group of a formula: NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a hydrogen atom, or a C_1–C_6 lower alkyl group; R^4 is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, benzodioxoyl, or a substituted group presented by structures (a), (b), (c) or (d) wherein R^8 through R^{12} identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1–C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)nR^5$, a group of a formula NR^6R^7, a trifluromethoxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and R^{13} is a hydrogen atom, a halogen atom, a C_1–C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a trifluromethoxy group, a carboxyl group, or an acetyl group; or their pharmaceutically acceptable salts are disclosed. And also cyclooxygenase-2 inhibitor composition, which consists of an effective amount of a diarylbenzopyran derivative and pharmaceutically acceptable salts of diarylbenzopyran derivative and shows an excellent selective inhibition, is disclosed.

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DIARYLBENZOPYRAN DERIVATIVES AS CYCLOOXYGENASE-2 INHIBITORS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to diarylbenzopyran derivatives or their pharmaceutically acceptable salts and cyclooxygenase-2 inhibitor composition containing same.

2. Description of the Related Arts

Non-steroidal, antiinflammatory drugs(NSAIDs), which have been most prevalently used all over the world, have a problem of causing serious side-effects such as gastrointestinal tract or nephro-toxicity. NSAIDs inhibit the activity of cyclooxygenase(hereinafter "COX"), which is an enzyme involved in prostagladin synthesis, resulting in the inhibition of the biosynthesis of prostaglandin not only in inflammatory loci but also in stomach and kidney. It has been found that COX exists in the form of isoenzymes: COX-1 and COX-2[Cell, 83,345, (1995)]. COX-1 exists in normal cells and keeps cell homeostasis and controlls the function of stomach and kidney, while COX-2 is expressed by mitogens or cytokines in pain sites where inflammation and other immunoreactions occur[J. Biol. Chem., 271,33157(1996)] and is involved in pathologic phenomenon. Therefore the toxicity of NSAIDs is due to its inhibition of the coexisting COX-1's.

To avoid this problem, selective inhibitors of COX-2 has been investigated[Nature, 367, 215(1995)]. The selective inhibitors (i) have suitable antiinflammation, pain-relieving action, antipyretic action; (ii) remove toxicity from and reduce bleeding time in gastrointestinal tract and kidney; (iii) show potential anticancer activity and reduce the induction of mechanism-related side-effect; and also (iv) lower the induction of asthma in asthmatic patients who are sensitive to conventional NSAIDs. These selective inhibitors of COX-2 also show

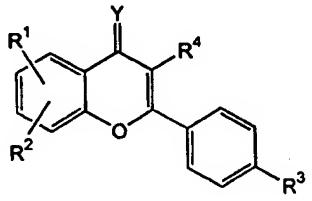
inhibition effect on smooth muscle constriction and could be used in treating Alzheimer's disease and osteoporosis of women after menopausa.

Active researches have been made on the selective inhibitors of COX-2. For example, WO 9606840, Bioorg, Med. Chem. Lett. 5, 2377(1995), Ann. Report. Med. Chem., 211(1997) and many other publications report COX-2 inhibitors having heterocyclic moiety as a base structure.

The present inventors made extensive researches to provide a new compound capable of inhibiting the COX-2's action selectively and strongly, and as a result found out that the diarylbenzopyran derivatives fulfill the requirements.

SUMMARY OF THE INVENTION

Therefore, an object of the present invention is to provide diarylbenzopyran derivatives represented by the following general formula (I) :



(I)

wherein

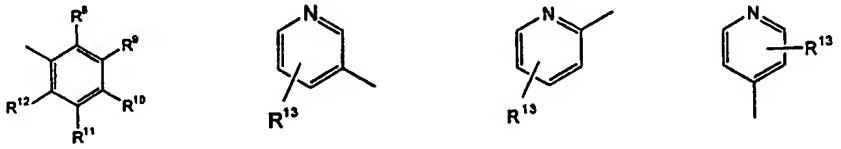
Y is an oxygen atom or a sulfur atom;

R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometlhyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^3 is a group of a formula : $S(O)nR^5$ wherein n is an integer of $0 \sim 2$, R^5 is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula : NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a

hydrogen atom, or a C_1 -C_6 lower alkyl group; and

R_4 is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, benzodioxolyl, or a substituted group presented by the following structures :



, , or

wherein

R^8 through R^{12} , identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula : S(O)nR^5, a group of a formula : NR^6 R^7 , a trifluromethoxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group, wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and

R^{13} is a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluromethyl group, a alkoxy group, a hydroxy group, a trifluromethoxy group, a carboxyl group, or an acetyl group;

or their pharmaceutically acceptable salts.

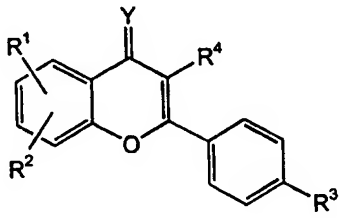
Another object of the present invention is to provide a cyclooxygenase-2 inhibitor composition comprising an effective amount of a compound represented by the above general formula(I) or pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The diarylbenzopyran derivatives or their pharmaceutically acceptable salts of the present invention effectively and selectively inhibit COX-2's action of

biosynthesizing the prostagladin, which plays a more important role in progress of inflammation than COX-1.

The diarylbenzopyran derivatives of the present invention, which are useful as selective COX-2's inhibitor drugs, are represented by the following general formula(I) :



(I)

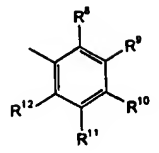
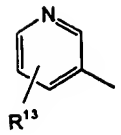
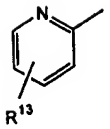
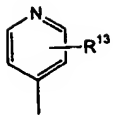
wherein

Y is an oxygen atom or a sulfur atom;

R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^3 is a group of a formula : $S(O)nR^5$ wherein n is an integer of $0 \sim 2$, R^5 is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula : NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a hydrogen atom, or a C_1 -C_6 lower alkyl group;

R^4 is oxazolyl, benzo[b]thienyl, puranyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzopuranyl, benzodioxoyl, or a substituted group presented by the following structures :

, , or

wherein

R^8 through R^{12} , identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula : S(O)nR^5, a group of a formula : NR^6 R^7 , a trifluromethoxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group, wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and

R^{13} is a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a trifluromethyl group, a alkoxy group, a hydroxy group, a trifluromethoxy group, a carboxyl group, or an acetyl group.

Also, the diarylbenzopyran derivatives of the above-described general formula(I) could form pharmaceutically acceptable salts, which generally refer to the salts that could form alkaline-metal salts, acid-addition salts, or base-addition salts and are pharmaceutically acceptable because of their non-toxicity. The pharmaceutically acceptable acid-addition salts of the compound(I) are derived from the organic acid or inorganic acid. The inorganic acid used in the present invention, for example, is hydrochloric acid, bromic acid, iodic acid, nitric acid, carbonic acid, sulfuric acid or phosphoric acid. The organic acid used in the present invention, for example, is formic acid, acetic acid, propionic acid, succinic acid, aspartic acid, ascorbic acid, benzoic acid, benzenesulfonic acid, methylsulfonic acid, p-toluenesulfonic acid or salicylic acid.

The pharmaceutically acceptable base-addition salts of the compound(I) are metal salts derived from Al, Ca, Li, Mg, K, Na and Zn or organic salts derived from N, N^{9}-dibenzylethylenediamine, choline, chloroprocaine, diethanolamine, ethylenediamine, N-methylglucamine and procaine.

Even though the use of diarylbenzopyran derivatives(I) of the present invention is not particulary limited, it is useful for treating, for example inflammatory diseases, or as analgesia for labor pain, headache or as antifebrile. The compound(I) of the present invention, not particularly limited, is also useful for treating arthritis such as rheumatic arthritis, spondylitis ankylopoietica, gouty arthritis, osteoarthritis. And the compound(I) of the present invention is useful for treating asthma, bronchitis, dysmenorrhea, tendinitis, bursitis and also useful for treating skin-related diseases such as psoriasis, eczema, burn and dermatitis. Also, the compound(I) of the present invention is useful for treating diseases such as peptic ulcer, gastritis, topical enteritis, colic diverticulitis, gastrointestinal bleeding, and the like. Also the compound(I) of the present invention coud be used in treating cancer by inhibiting the transformation of cell and the growth of metastatic cancer. Moreover, it could be used in treating and preventing diseases, which show abnormality in cyclooxygenase-involving proliferation such as diabetic retinopathy and cancerous vascularization. And it is effective in treating Alzheimer^{9}s disease and used in preventing osteoporosis and in treating glaucoma.

Also, the compound(I) of the present invention could be used as a substitute drug for conventional non-steroidal antiinflammatory drugs because it shows high activity and specificity on COX-2. Particulary, the compound of the present invention could be used as a substitute drug in treating patients who are suffering from hypoprothrombinemia, hemophilia or kidney disease, or waiting for surgery or has recurrent gastrointestinal tract disorders such as agglutination abnormality cause by anticoagulant uptake.

In addition to that the compound of the present invention, as we described above, is useful for treating human diseases, it also could be used in treating warm-blooded animals such as mice, house mice, horses, lambs, dogs, cats and etc.

Also, the compound(I) of the present invention could be used as a whole or partial substitute for the preparations containing the existing non-steroidal inflammatory drugs. In other words, diarylbenzopyran derivatives or their pharmaceutically acceptable salts could be used alone or combined with one of or some of the following components:

(i) pain relievers containing acetoaminophen or phenacetin;

(ii) potentiators containing caffeine;

(iii) H_2-antagonists;

(iv) decongestants containing aluminum hydroxide, magnesium hydroxide, simethicone, phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, propylhexedrine or levodeoxyephedrine;

(v) antitussives containing codeine, hydrocodone, caramiphene, carbetapentane or dextramethorphan;

(vi) prostaglandins containing misoprostol, enprostil, riprostil, ornoprostol or rosaprostol;

(vii) diuretics;

(viii) antihistamines having or without having sedative action.

The preferred compound(I) of the present invention includes one of the following compounds :

2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-(N,N-Dimethylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-(N-Methylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethoxyphenyl)-4H-1-benzopyran-4-one,
3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Isopropylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Ethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Hydroxymethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one,
3-(4-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,3-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3,5-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Acetylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,4-Dimethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Formylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Carboxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Chloro-3-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-5-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-5-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3,5-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(N-methyl-3-pyrazolyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-Chloro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
2-(4-(methylsulfonyl)phenyl)-3-(3-nitrophenyl)-4H-1-benzopyran-4-one,
3-(3,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(methylsulfonyl)phenyl)-3-(1-naphthyl)-4H-1-benzopyran-4-one,
3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Bromophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-oxazolyl)-4H-1-benzopyran-4-one,
6-Fluoro-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Benzo[b]thienyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

7-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(1,3-Benzodioxol-5-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-thiazolyl)-4H-1-benzopyran-4-one,

3-(Benzofuran-2-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-pyrazinyl)-4H-1-benzopyran-4-one,

3-(2-Methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-Fluoro-3-(2-methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-6-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

7-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-

4-one,
3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-trifluoromethyl-5-pyridinyl)-4H-1-benzopyran-4-one,
3-(2-Fluoro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Bromo-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Furyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Indanyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methyl-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
3-(4-Fluorophenyl)-6-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chloro-3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chloro-4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-((4-methylthio)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-((3,4-methylenedioxy)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2,3-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2,4-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-methylphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxyphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(4-methylphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-methoxyphenyl)-4H-1-benzopyran-4-one,.

2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-7-fluoro-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3,5-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-6-fluoro-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methyl-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-furyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-hydroxy-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-methoxy-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-7-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-6-hydroxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,

3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 - thione,

3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-thione,

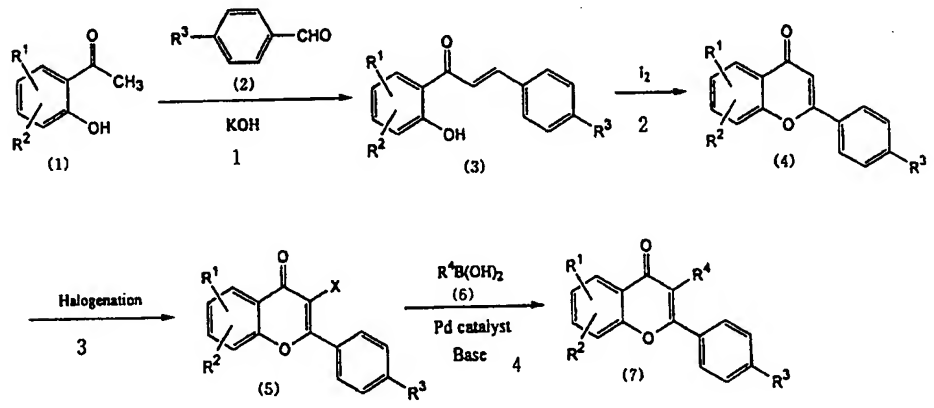
3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 - thione,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione

The diarylbenzopyran derivatives of the present invention can be prepared by reaction schemes 1 through 6. Wherein R^1, R^2, R^3 and R^4 in the reaction schems have the same meanings as defined above.

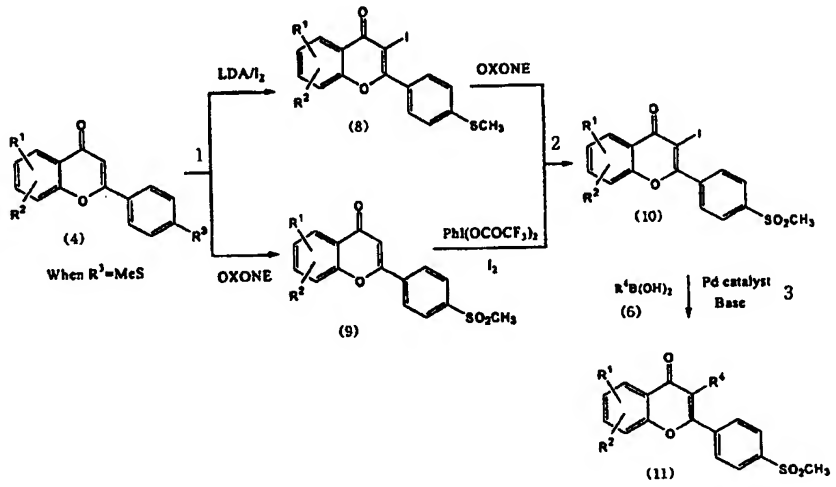
[Reaction Scheme 1]



It represents a four-step reaction of preparing diarylbenzopyran derivative. In Step 1, chalcone(3) is prepared by condensation of substituted acetophenon(1) and substituted aldehyde(2) in the presence of KOH base. In Step 2, flavone

derivative is prepared by cyclization of calcone(3) by adding I_2 as a catalyst. A suitable solvent of this step is dimethyl sulfoxide(DMSO). In Step 3, 3-halogenized flavone derivative is prepared by reaction of flavone derivative(4) either with I_2 or N-bromosuccinimide(NBS). In Step 4, benzopyran derivative(7) in which R^4 group at position 3 is substituted is prepared by cross-coupling reaction of substituted flavone derivative(5) with R^4 group substituted boronic acid using Paladium as a catalyst[(Synth. Commun., 11, 513(1981)].

[Reaction Scheme 2]

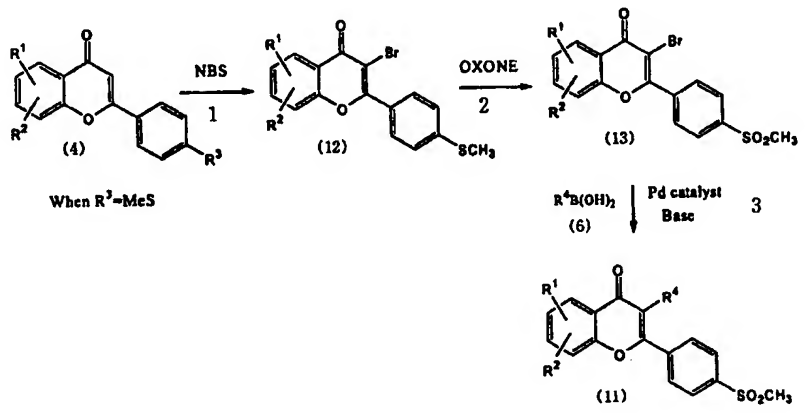


It represents a 3-step transformed reaction of preparing diarylbenzopyran derivative. In Step 1, compound(8) is prepared by the reaction of flavone derivative(4) having methylthio group as R^3 with I_2 in the presence of Lithium diisopropylamide(LDA) base, at a temperature of -78 ℃[J. Chem. Soc. Perkin Trans. I. 799(1985)]. In Step 2, methylsulfonylflavone(10) is prepared by oxidation with oxone(potassium peroxymonosulfate) or 3-chloroperoxybenzoic acid(MCPBA). In Step 3, benzopyran derivative(11) is prepared by cross-

coupling reaction of compound(10) with boronic acid(6) using paladium as catalyst.

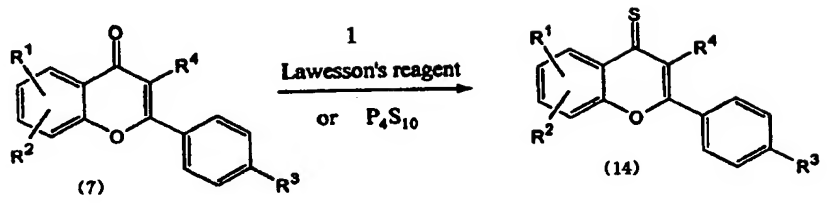
Alternatively, compound(11) could be prepared by the following method: First, methylsulfonyl group substituted flavone derivative(9) is prepared by oxidizing compound(4) having methylthio group as R^3 with oxone; and then compound(10) is prepared by reacting compound(9) with I_2 and [Bis(trifluoroacetoxy)iodo]benzene(BTI); and benzopyran derivative(11) is prepared by Step 3 of the above reaction.

[Reaction Scheme 3]



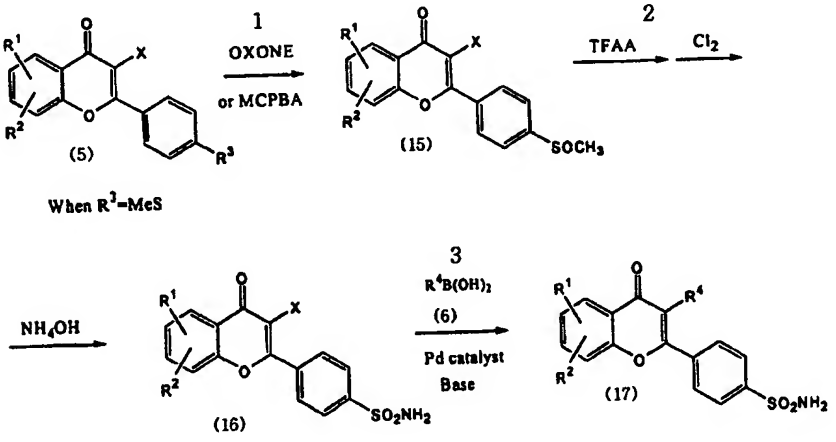
It represents the 3-step modified reaction of preparing diarylbenzopyran derivative. In Step 1, bromoflavone(12) is prepared by refluxing flavone derivative(4) having methylthio group as R^3 in chloroform in the presence of N-bromosuccinimide(NBS). In Step 2, methylsulfonylflavone(13) is prepared by oxidation with oxone or MCPBA. In Step 3, benzopyran derivative(11) is substituted is prepared by cross-coupling reaction of compound(13) with boronic acid(6) using paladium catalyst.

[Reaction Scheme 4]



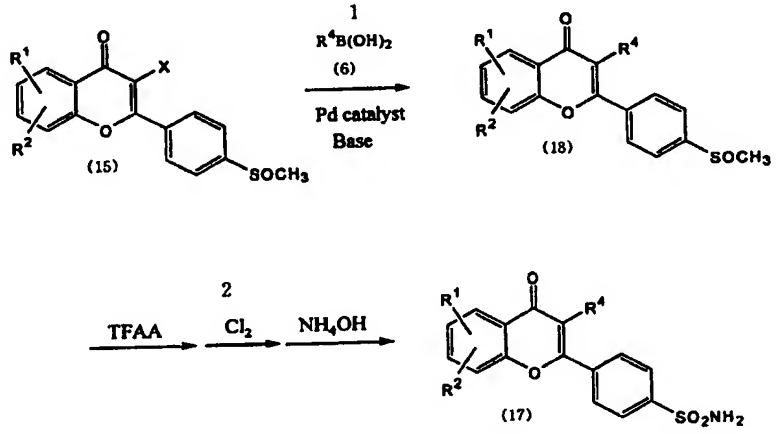
It represents the 1-step reaction of preparing diarylbenzopyranthione derivative. Benzopyranthione derivative(14) is prepared by refluxing diarylbenzopyran derivative with Lawesson reagent(2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphentan-2,4-disulfate; Org. Synth. Coll., 7, 372(1990)) or P_4S_{10} in toluenet.

[Reaction Scheme 5]



It represents the 3-step reaction of preparing diarylbenzopyran derivative. In Step 1, methylsulfinylflavone derivative(15) is prepared by oxidizing compound(5) with oxone or MCPBA. In Step 2, aminosulfonylflavone derivative is prepared by reacting flavone derivative(15) with trifluoroacetic anhydride(TFAA), chlorine gas, ammonium hydroxide. In Step 3, benzopyran derivative(17) is prepared by cross-coupling reaction of aminosulfonylflavone deriative(16) with boronic acid(6) using paladium catalyst.

[Reaction Scheme 6]



It represents the modified reaction of preparing diarylbenzopyran derivative. In Step 1, benzopyran derivative(18) is prepared by cross-coupling reaction of flavone derivative(15) prepared in reaction scheme 5, Step 1 with boronic acid(6) using paladium catalyst. In next step, benzopyran derivative(17) is prepared by having the same condition of the reaction scheme 5, Step 2.

The present invention will be described in more detail by the following examples and experimental examples, but it must not to be construed that this

invention is confined by them.

[Example 1] 3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzo -pyran-4-one

Step 1; 2'-Hydroxy-4-(methylthio)chalcone

To a solution of 2'-hydroxyacetophenone(10.88g, 80mmol) and 4-(methylthio)benzaldehyde(12.16g, 80mmol) in ethanol(120㎖) at a temperature of 0℃ was added a solution of KOH (8.96g, 2.0 equivalent) in water(40㎖) dropwise. The mixture was stirred at room temperature for 24 hours. The solution was acidified with 3N HCl(88㎖) and extracted two times with CH_2Cl_2 (100㎖ per each). The organic layer was washed with saturated NaCl and dried over anhydrous $MgSO_4$ and filtered and concentrated under reduced pressure. The recrystallization of the residue with CH_2Cl_2 and petroleum ether yielded the title compound as a yellow solid (42.01g, 65%).

mp: 98～100℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.94～7.86(2H, m), 7.65～7.47(6H, m), 7.29～7.25(2H, m), 7.05～6.92(2H, m), 2.53(3H, s)

IR(KBr): 2911, 1658, 1433, 1306, 1090, 1013㎝$^{-1}$

Step 2 : 2-(4-(Methylthio)phenyl)-4H-1-benzopyran-4-one

2'-hydroxy-4-(methylthio)chalcone(9.5g, 35.15mmol) from Step 1 and catalytic amount of I_2 was dissolved in dimethylsulfoxide(;DMSO, 100㎖) and the resulting mixture was stirred at a temperature of 180℃ for half an hour. After identifying the reaction being complete by TLC, the resulting dark solution was poured into excessive ice-water(about 300㎖) and stirred for 10 minutes. The mixture was extracted two times with CH_2Cl_2 (100㎖ per each). And the organic

layer was washed with saturated $Na_2S_2O_3$(100㎖) , brine and dried over anhydrous $MgSO_4$ and filtered and concentrated under reduced pressure. The recrystallization of the residue with CH_2Cl_2 and petroleum ether yielded the title compound as a light yellow solid(7.54g, 80%).

mp : 110～112℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.25～8.22(m, 1H), 7.86～7.83(m, 2H), 7.73～7.66(1H, m), 7.58～7.55(m, 1H), 7.45～7.40(1H, m), 7.37～7.33(2H, m), 6.83(1H, s), 2.55(3H, s)

IR(KBr): 1654, 1594, 1464, 1379, 1099㎝$^{-1}$

Step 3: 3-Iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

To a solution of 2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.20g, 0.75mmol) from Step 2 in anhydrous tetrahydrofuran(THF, 15㎖) was added 2M LDA (0.38㎖, 1 equivalent) by syringe with stirring at a temperature of -78℃ for 15 minutes under Argon gas atmosphere and then iodine(0.19g, 0.75mmol) in THF(5㎖) was added. The mixture was warmed to room temperature and then stirred for 12 hours. After the reaction being complete, the reaction mixture was poured into saturated $Na_2S_2O_3$(100㎖) and stirred for 1 hour, and the mixture was extracted two times with CH_2Cl_2 (30㎖ per each) and the organic layer was washed with brine and dried over anhydrous $MgSO_4$ and filtered. The residue was subjected to flash chromatography using a mixture of hexane :ethyl acetate(7 : 1) as an eluant to afford the title compound as a pale yellow solid(0.23g, 78%).

mp: 150～152℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.30～8.27(1H, m), 7.77～7.74(2H, m), 7.73～7.70(1H, m), 7.51～7.44(2H, m), 7.38～7.35(2H, m), 2.57(3H, s)

IR(KBr): 3032, 2912, 1646, 1599, 1490, 1330, 1060, 752㎝$^{-1}$

Step 4: 3-Iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

To a solution of 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.34g, 0.86mmol) from Step 3 in MeOH(10㎖) and THF(10㎖) was added a solution of Oxone (1.59g, 2.59mmol) in H_2O(10㎖) dropwise at a temperature of 0 ℃. The resulting mixture was stirred for 3 hours. And the solution was extracted two times with CH_2Cl_2 (20㎖ per each), and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. And the resulting solution was filtered and concentrated under reduced pressure. Recrystallization of the resulting residue with CH_2Cl_2 and petroleum ether yielded the title compound as a white solid(0.33g, 90%)

mp: 164～165℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33～8.29(1H, m), 8.15～8.12(2H, m), 8.03～7.99(2H, m), 7.80～7.74(1H, m), 7.53～7.49(2H, m), 3.16(3H, s)

IR(KBr): 1643, 1470, 1301, 1151, 960, 750 cm^{-1}

Step 5: 3-(4-Fluorophenyl)-2-(4-methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

To a solution of 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one (0.33g, 90%) from Step 4, 4-fluorobenzeneboronic acid(0.036g, 0.26mmol) in toluene(1㎖) and EtOH(1㎖) was added 2M aqueous sodium carbonate (0.61㎖) and then tetrakis(triphenylphosphine)palladium(0.014g, 0.012mmol) and was stirred at a temperature of 90℃ for 4 hours. After being concentrated under reduced pressure, it was dissolved in dichloromethane(10㎖) and washed with water, brine. The organic layer was dried over anhydrous $MgSO_4$. And the resulting solution was filtered and concentrated under reduced pressure. The residue was subjected to flash chromatography using a mixture of hexane :ethyl acetate(1 : 1) as an eluant to yield the title compound as a pale yellow solid(0.046g,

59%).

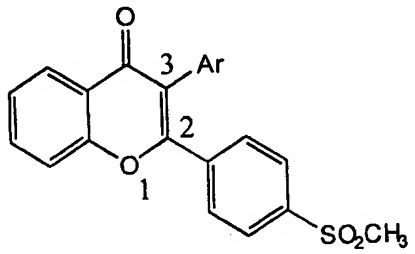
mp: 208~210℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.30(1H, m), 7.90~7.87(2H, d), 7.79~7.73(1H, m), 7.62~7.60(2H, d), 7.57~7.54(1H, d), 7.51~7.46(1H, m), 7.21~7.16(2H, m), 7.07~7.01(2H, m), 3.07(3H, s)

IR(KBr): 3017, 2922, 1640, 1509, 1468, 1378, 1290, 1230, 1155, 1142, 770 cm^{-1}

[Example 2 - 21]

The inventive compounds of Examples 2 - 21 were produced by the same procedure described in Example 1, but substituting appropriate boronic acid or boronate for 4-fluorobenzeneboronic acid in Example 1, step 5. These compounds and their physical properties are shown in Table 1.



<Table 1>

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
2	phenyl	208-209	8.34～8.31(1H,m), 7.88～7.85(2H,m), 7.79～7.74(1H,m), 7.64～7.55(3H,m), 7.51～7.46(1H,m), 7.36～7.33(3H,m), 7.23～7.20(2H, m), 3.06(3H, s)	3020, 2923, 1621, 1467, 1378, 1295, 1152
3	4-methylphenyl	225	8.32～8.29(1H,m), 7.88～7.85(2H,d), 7.77～7.71(1H,m), 7.64～7.62(2H,d), 7.56～7.44(2H,m), 7.16～7.07(4H,m), 3.06(3H,s), 2.36(3H, s)	1644, 1377, 1297
4	3-nitrophenyl	223-224	8.33～8.30(1H,m), 8.22～8.18(1H,m), 8.10(1H,m), 7.93～7.90(2H,m), 7.83～7.77(1H,m), 7.63～7.49(6H,m), 3.06(3H,s),	3080, 2914, 1640, 1526, 1462, 1350, 1143
5	2, 4-dichlorophenyl	172-175	8.32～8.29(1H,m), 7.93～7.91(2H,m), 7.81～7.75(1H,m), 7.66～7.63(2H,m), 7.59～7.47(3H,m), 7.11～7.09(1H,d), 3.07(3H,s)	1642, 1472, 1302, 1145, 774
7	2-thienyl	165-167	8.33～8.30(1H,m), 8.15～8.12(2H,m), 8.02～7.99(2H,m), 7.95～7.93(1H,m), 7.80～7.72(2H,m), 7.55～7.46(3H,m), 3.16(3H,s)	1668, 1300, 1157
8	4-acetylphenyl	223-224	8.33～8.30(1H,m), 7.95～7.86(4H, m); 7.81～7.75(1H,m), 7.63～7.59(2H, m), 7.56(1H, s), 7.53～7.47 (1H, m), 7.36～7.32(2H, m), 3.07(3H, s), 2.62(3H, s)	1690, 1646, 1376, 1142
9	4-formylphenyl	189-190	10.03(1H, s), 8.33～8.29(1H, m), 7.90～7.84(4H,m), 7.80～7.75(1H, m), 7.63～7.60(2H,m), 7.57(1H, s), 7.53～7.48(2H, m), 7.43～7.39(2H,m), 3.07(3H, s)	2925, 1642, 1466, 1379, 1301, 1143
10	4-methoxyphenyl	212-213	8.32～8.29(1H,m), 7.89～7.86(2H, d), 7.77～7.71(1H,m), 7.65～7.62 (2H,d), 7.56～7.53(1H,d), 7.47 (1H, t), 7.14～7.11(2H, d), 6.89 ～6.86(2H, d), 3.82(3H, s), 3.06(3H, s)	3006, 2915, 1632, 1608, 1513, 1465, 1376, 1300, 1141

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
11	3,4-dichlorophenyl	164-165	8.31～8.28(1H,m), 7.95～7.92(2H,m), 7.80～7.74(1H,m), 7.65～7.62(2H, m), 7.58～7.50(2H,m),7.41～7.37(2H, m), 7.03～7.00(1H,m), 3.08(3H, s)	1643, 1619, 1470, 1301, 1151
12	2-fluorophenyl	180-181	8.33～8.30(1H,m),7.90～7.87(2H,m),7.79～7.74(1H m), 7.66～7.63 (2H, m), 7.58～7.46(2H, m), 7.40～7.32(1H,m), 7.24～7.20(3H, m) , 3.06(3H, s)	3089, 2931, 1640, 1469, 1376, 1300, 1142, 769
13	1-naphthyl	193-194	8.34～8.30(1H,m),7.91～7.77(3H, m),7.74～7.61(4H, m), 7.54～7.43 (5H, m), 7.44～7.36(1H, m), 7.20～7.17(1H, m), 2.96(3H, s)	2925, 1638, 1464, 1317, 1156, 764
14	2, 3-dichlorophenyl	135-137	8.32～8.29(1H,m), 7.93～7.91(2H,m), 7.81～7.75(1H,m), 7.66～7.63(2H,m), 7.59～7.47(3H,m), 7.11～7.09(1H,d), 3.07(3H,s)	1642, 1607, 1468, 1381, 1309, 1145, 772
15	3-pyridinyl	220-221	8.57～8.54(1H,m),8.33～8.29(2H,m), 7.92～7.88(2H,m),7.82～7.70 (2H, m), 7.62～7.48(4H, m), 7.37～7.34(1H,m), 3.07(3H, s)	3052, 2923, 1639, 1466, 1381, 1301, 1156, 787
16	4-pyridinyl	204-205	8.61～8.58(2H,m),8.33～8.29(1H,m), 7.93～7.89(2H, m), 7.82～7.75 (1H, m), 7.64～7.48(4H, m), 7.18～7.15(2H, m), 3.07(3H, s)	2990, 1642, 1467, 1382, 1302, 1145, 784
17	N-methyl-3-pyrazolyl	202-203	8.31～8.28(1H,m),8.01～7.98(2H,m), 7.83～7.79(3H,m),7.75～7.69(1H,m), 7.52～7.43(2H,m),6.97～6.96(1H,m), 3.91(3H,s), 3.07(3H, s)	3091,2925, 1641,1467, 1313,1154, 766
18	2-methoxy-5-pyridinyl	226-227	8.31～8.28(1H,m),7.93～7.86(3H,m), 7.79～7.73(1H,m), 7.66～7.63 (2H, m), 7.60～7.45(3H, m), 6.80～6.77(1H, m), 3.92(3H, s), 3.09(3H, s)	3054,2924, 1641,1601, 1496,1466, 1369,1301, 1144,769
19	5-bromo-3-pyridinyl	197-199	8.62～8.60(1H,m),8.31～8.28(1H,m), 8.18～8.16(1H,m),7.96～7.93(2H,m), 7.83～7.76(1H, m), 7.64 ～7.49(5H, m), 3.09(3H, s)	3065,2925, 1613,1466, 1378,1315, 1153,765

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
20	2-methyl-5-pyridinyl	195-196	8.31～8.28(1H,m), 8.21～8.19(1H,m), 7.92～7.88(2H,m), 7.79～7.73 (1H, m), 7.63～7.46(5H, m), 7.21～7.18(1H, m), 3.08(3H, s), 2.57(3H, s)	2924,1641, 1466,1400, 1301,1144, 764
21	2-trifluoromethyl-5-pyridinyl	215-217	8.44～8.43(1H,m), 8.33～8.29(1H,m), 7.96～7.92(2H,m), 7.84～7.72 (2H, m), 7.63～7.50(5H, m), 3.10(3H, s)	3050,1645, 1467,1337, 1145,1088, 761

[Example 22] 3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Step 1; 3-Bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

A solution of (4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.50g, 1.86mmol) and NBS(0.36g, 2.05mmol) in $CHCl_3$(30㎖) was heat to reflux for 5 hours. The resulting mixture was washed with saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$, and filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography using a mixture of hexane : ethyl acetate(4 : 1) as an eluant to yield the title compound as a pale yellow solid(0.60g, 93%).

mp: 162～163℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.30～8.27(1H, m), 7.84～7.80(2H, m), 7.74～7.69(1H, m), 7.51～7.43(2H, m), 7.38～7.34(2H, m), 2.55(3H, s)

IR(KBr): 1658, 1611, 1463, 1331, 1065, 753 cm^{-1}

Step 2; 3-Bromo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2 -(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-bromo-2-(4-(methylthio)- phenyl)-4H-1-benzopyran-4-one(0.6g, 0.86mmol) from Step 1, the

title compound was obtained as a solid(0.59g, 90%).

mp: 211~213℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.34~8.30(1H, m), 8.15~8.05(4H, m), 7.80~7.74(1H, m), 7.54~7.49(2H, m), 3.15(3H, s)

IR(KBr): 1646, 1310, 1146, 1075 cm^{-1}

Step 3; 3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3-bromo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one(0.18g, 0.47mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and *m*-tolylboronic acid(0.071g, 0.52mmol) for 4-fluorobenzeneboronic acid, the title compound was obtained as a solid(0.13g, 70%).

mp: 178~179℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.31~8.29(1H, m), 7.87~7.84(2H, m), 7.76~7.72(1H, m), 7.64~7.61(2H, m), 7.56~7.44(2H, m), 7.22~7.06(2H, m), 6.96~ 6.93(1H, m), 3.05(3H, s), 2.31(3H, s)

IR(KBr): 2920, 1639, 1465, 1377, 1299, 1149, 771 cm^{-1}

[Example 23] 3-(2-Methylphenyl)-2-(4-(methylsulfonl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by *o*-tolylboronic acid, the title compound was obtained as a solid.

mp: 190~191℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.29(1H, m), 7.86~7.83(2H, m), 7.79~ 7.74(1H, m), 7.60~7.57(3H, m), 7.51 ~ 7 .46(1H, m), 7.28~7.26(2H, m),

7.18～ 7.16(1H, m), 7.01～6.99(1H, m), 3.04(3H, s), 2.15(3H, s)

IR(KBr): 1618, 1376, 1324, 1156, 766 cm^{-1}

[Example 24] 3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1 -benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by 3-chlorobenzeneboronic acid, the title compound was obtained as a solid.

mp: 195～196℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32～8.27(1H, m), 7.91～7.89(2H, m), 7.80～ 7.74(1H, m), 7.64～7.61(2H, m), 7.58 ～7.49(2H, m), 7.31～7.28(2H, m), 7.26 ～7.25(1H, m), 7.07～70.5(1H, m), 3.07(3H, s)

IR(KBr): 1645, 1466, 1377, 1141 cm^{-1}

[Example 25] 3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by 3-fluorobenzeneboronic acid, the title compound was obtained as a solid.

mp: 225℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.36～8.33(1H, m), 7.91～7.89(2H, m), 7.80～ 7.73(1H, m), 7.64～7.61(2H, m), 7.58 ～7.46(2H, m), 7.34～7.28(2H, m), 7.08～ 6.97(2H, m), 3.07(3H, s)

IR(KBr): 3022, 1646, 1468, 1379, 1296, 1142, 770 cm^{-1}

[Example 26] 3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl) -4H-1-benzopyran-4-one

Following the procedure of Example 22, Step 3, but replacing *m*-tolylboronic acid by 3-chloro-4-fluorobenzeneboronic acid, the title compound was obtained as a solid.

mp: 196℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.25(1H, m), 7.94~7.91(2H, m), 7.80~7.75(1H, m), 7.65~7.61(2H, m), 7.58~7.47(2H, m), 7.34~7.31(1H, m), 7.13~7.01(2H, m), 3.08(3H, s)

IR(KBr): 1618, 1466, 1375, 1301, 1144, 761 cm^{-1}

[Example 27] 3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Step 1; 3-(4-Chlorophenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3-bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.1g, 0.29mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl) and 4-chlorobenzeneboronic acid(0.05g, 0.32mmol) for 4-fluorobenzeneboronic acid, the title compound was obtained as a solid(0.02g, 20%).

mp: 145~147℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.30~8.26(1H, m), 7.73~7.72(1H, m), 7.55~7.44(3H, m), 7.33~7.29(3H, m), 7.20~7.12(4H, m), 2.48(3H, s)

IR(KBr): 1636, 1594, 1465, 1092 cm^{-1}

Step2;3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-(4-chlorophenyl)-2-(4-

(methylthio)phenyl)-4H-1-benzopyran-4-one(0.05g, 0.12mmol), the title compound was obtained as a solid(0.048g, 89%).

mp: 187~188℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 7.91~7.89(2H, m), 7.79~7.73(1H, m), 7.63~7.61(2H, m), 7.57~7.46(2H, m), 7.34~7.27(2H, m), 7.17~7.14(2H, m), 3.08(3H, s)

IR(KBr): 3083, 2926, 1617, 1465, 1377, 1301, 1157, 1091, 770 cm^{-1}

[Example 28] 3-(4-Bromophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-(4-bromophenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one (0.06g, 0.14mmol), the title compound was obtained as a solid(0.059g, 90%).

mp: 168~170℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 7.92~7.89(2H, m), 7.77~7.73(1H, m), 7.63~7.46(6H, m), 7.11~7.08(2H, m), 3.08(3H, s)

IR(KBr): 3027, 2925, 1640, 1465, 1375, 1300, 1142, 772 cm^{-1}

[Example 29] 2-(4-(Methylthio)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3-bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.1g, 0.32mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and 4-trifluoromethylbenzeneboronic acid(0.066g, 0.35mmol) for 4-fluorobenzeneboronic acid, the title compound was obtained as a solid(0.05g, 40%).

mp: 189~192℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.31~8.27(1H, m), 7.77~7.70(1H, m), 7.61~7.54(3H, m), 7.49~7.43(1H, m), 7.39~7.36(2H, m), 7.31~7.28(2H, m), 7.15~7.11(2H, m), 2.48(3H, s)

IR(KBr): 2870, 1663, 1425, 1295, 1010 cm^{-1}

[Example 30] 2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 2-(4-(methylthio) phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one(0.027g,0.065mmol), the title compound was obtained as a solid(0.03g, 100%).

mp: 213~216℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33~8.29(1H, m), 7.92~7.88(2H, m), 7.81~7.75(1H, m), 7.63~7.47(6H, m), 7.37~7.34(2H, m), 3.08(3H, s)

IR(KBr): 2927, 1641, 1455, 1378, 1325, 1143, 1109, 1017, 771 cm^{-1}

[Example 31] 3-(3,5-Dichlorophenyl)-2-(4-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

Step 1; 3-(3,5-Dichlorophenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting 3,5-dichlorobenzeneboronic acid(0.067g, 0.35mmol) for 4-fluorobenzeneboronic acid and 3-bromo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.1g, 0.29mmol) for 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one, the title compound was obtained as a solid(0.043g, 36%).

mp: 198~200℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.29~8.25(1H, m), 7.77~7.70(1H, m), 7.57~7.43(2H, m), 7.35~7.14(5H, m), 6.94~6.92(1H, m), 6.75~6.74(1H, m), 2.50(3H, s)

IR(KBr): 2880, 1650, 1430, 1253, 950 cm^{-1}

Step 2 ; 3-(3,5-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzo-pyran-4-one

Following the same oxidation procedure of Example 1, Step 4, but replacing 3-iodo-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by 3-(3,5-dichloro-phenyl)-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(0.04g, 0.096mmol), the title compound was obtained as a solid(0.02g, 47%).

mp: 258~260℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 7.97~7.93(2H, m), 7.81~7.75(1H, m), 7.66~7.62(2H, m), 7.59~7.48(2H, m), 7.35~7.33(1H, m), 7.11~7.10(2H, m), 3.08(3H, s)

IR(KBr): 3011, 2920, 1628, 1580, 1453, 1373, 1305, 1299, 1155, 961, 764 cm^{-1}

[Example 32] 3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and 3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)-phenyl)-4H-1-benzopyran-4-one

Step 1 ; 2-(4-(Methylsulfonyl)phenyl)-3-(N-oxo-3-pyridinyl)-4H-1-benzopyran-4-one

A solution of 2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one(0.2g, 0.54mmol) from Example 15 and MCPBA(0.18g, 0.6mmol) in CH_2Cl_2(20mL) was refluxed for 1.5 hours. Then the mixture was

cooled to room temperature and washed with 1N NaOH solution. The organic layer was dried and concentrated *in vacuo* to yield the title compound as a pale yellow solid(0.2g).

mp: 231-232℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32~8.28(1H, m), 8.18~8.15(1H, m),8.04~8.03(1H, m), 7.99~7.95(2H, m), 7.83~7.76(1H, m), 7.69~7.65(2H, m), 7.60~7.50(2H, m), 7.33~7.21(2H, m), 3.11(3H, s)

IR(KBr): 2923,1641,1467,1385, 1303,1261,1144,760 cm^{-1}

Step 2 ;

compound A; 3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

compoundB;3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)-phenyl)-4H-1-benzopyran-4-one

A solution of 2-(4-(methylsulfonyl)phenyl)-3-(N-oxo-3-pyridinyl)-4H-1-benzopyran-4-one(0.2g, 0.51mmol) in $POCl_3$(2mL) was heated at a temperature of 110 ℃ for 6.5 hours. After evaporating the excess $POCl_3$, the residue was poured into ice and made alkaline with NH_4OH and extracted with CH_2Cl_2. After the solvent being evaporated, the residue was subjected to flash chromatography to yield the title compound as a pale yellow solid(A; 0.092g, B; 0.03g).

compound A;

mp: 232-233℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.31~8.28(1H, m), 8.14~8.06(2H, m), 7.96~7.93(2H, m), 7.82~7.75(1H, m), 7.73~7.69(1H, m), 7.64~7.48(4H, m), 7.42~7.36(1H, m), 3.09(3H, s)

IR(KBr): 2920,1647,1465,1308,1140,760 cm^{-1}

compound B;

mp: 235-236℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.51~8.49(1H, m), 8.33~8.29(2H, m), 7.92~7.89(2H, m), 7.83~7.76(1H, m), 7.63~7.42(5H, m), 3.06(3H, s)

IR(KBr): 2925,1643,1466,1307,1145,767 cm^{-1}

[Example 33] 2-(4-(Methylsulfonyl)phenyl)-3-(2-pyridinyl)-4H-1 -benzopyran-4-one

A solution of 3-bromo-2-(4-(methylsulfonyl)phenyl)-4H-1 -benzopyran-4 -one (0.5g, 1.32mmol) from Example 22, Step 2 and 2-tributylstannylpyridine(0.58g, 1.58mmol) and tetrakis(triphenylphosphine)palladium(0.15g, 0.13mmol) in N-methyl-2-pyrrolidine(50㎖) and ethanol(1㎖) was heated at a temperature of 100℃ for 24 hours. Then the mixture was cooled to room temperature and diluted with ethyl acetate and filtered through a pad of celite. The mixture was washed with 5% aqueous KF, dried and concentrated. The residue was subjected to flash chromatography to yield the title compound as a pale yellow solid(0.27g).

mp: 203~204℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.55~8.52(1H, m), 8.33~8.29(1H, m),7.88~7.84(2H, m), 7.79~7.73(2H, m), 7.60~7.55(3H, m), 7.51~7.46(2H, m), 7.29~7.24(1H, m), 3.05(3H, s)

IR(KBr): 3058, 1642, 1467, 1382, 1303, 1146, 769 cm^{-1}

[Example34]6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one

Step 1; 5'-Fluoro-2'-hydroxy-4-(methylthio)chalcone

The title compound was prepared from 4-(methylthio)benzaldehyde and 5'-

fluoro-2'-hydroxyacetophenone by the same method as described in Step 1 of Example 1.

mp: 147~148℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.92(1H, d, J=15.6Hz), 7.61~7.57(3H, m), 7.50(2H, d, J=15.3Hz), 7.30~7.21(2H, m), 7.03~6.98(1H, m), 2.54(3H, s)

IR(neat): 1640, 1573, 1482, 1359, 1170, 1097, 776 cm^{-1}

Step 2 ; 6-Fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 5'-fluoro-2'-hydroxy-4-(methylthio)chcalcone and iodine by the same method as described in Step 2 of Example 1.

mp: 177~178℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.88~7.81(3H, m), 7.59~7.55(1H, m), 7.45~7.39(1H, m), 7.37~7.33(2H, m), 6.78(1H, s), 2.55(3H, s)

IR(neat): 1639, 1579, 1261,818 cm^{-1}

Step 3; 6-Fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 6-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one by the same method as described in Step 4 of Example 1.

^{1}H NMR($CDCl_3$, 300MHz): δ 8.16~8.08(4H, m), 7.91~7.87(1H, m), 7.65~7.60(1H, m), 7.51~7.44(1H, m), 6.89(1H, s), 3.12(3H, s)

Step 4: 6-Fluoro-3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran -4-one

A solution of 6-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one(3.5g, 11mmol) , iodine(2.8g, 11mmol) and [bis(trifluoroacetoxy)iodo]-benzene (3.5g, 11mmol) in CH_2Cl_2(250㎖) was stirred at room temperature for 24

hours. The resulting mixture was washed with saturated $Na_2S_2O_3$(100㎖), saturated $NaHCO_3$(100㎖) and then washed with brine and dried over anhydrous MgSO$_4$ and concentrated. Recrystallization of the resulting residue by CH_2Cl_2 and petroleum ether yielded the title compound as a white solid(2.5g, 71%).

^{1}H NMR($CDCl_3$, 300MHz): δ 8.14~8.10(2H, m), 8.01~7.91(3H, m),7.55~7.44(2H, m), 3.15(3H, s)

Step 5: 6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1 -benzopyran-4-one

The title compound was prepared from 6-fluoro-3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one and lithium trimethoxy-3-pyridinylboronate by the same method as described in Step 5 of Example 1.

mp: 233~234℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.60~8.54(1H, m), 8.36~8.28(1H, m), 7.96~7.88(3H, m), 7.77~7.73(1H, m), 7.62~7.47(4H, m), 7.40~7.34(1H, m), 3.07(3H, s)

IR(neat): 2928, 1642, 1483, 1272, 1152, 766 ㎝$^{-1}$

[Example 35] 6-Fluoro-3-(2-methyl-5-pyridinyl)-2-(4-(methylsulfonyl) -phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 34, Step 5, but substituting lithium trimethoxy-2-methyl-5-pyridinylboronate for lithium trimethoxy-3-pyridinylboronate, the title compound was obtained as a solid.

mp: 145-148℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.20~8.19(1H, m), 7.95~7.89(3H, m),7.63~7.45(5H, m), 7.23~7.20(1H, m), 3.08(3H, s), 2.58(3H, s)

IR(KBr): 2925,1613,1451,1315,1150,767 ㎝$^{-1}$

[Example 36] 3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione

A solution of 3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one(0.45g, 1.14mmol) from Example 1 and Lawesson's reagent(0.23g, 0.57mmol) in toluene(10㎖) was refluxed for 1 hour. The resulting mixture was concentrated and subjected to flash chromatography using a mixture of hexane :ethyl acetate: dichloroethane(1 : 1 :1) as an eluant to yield the title compound as a deep green solid(0.4g, 85%).

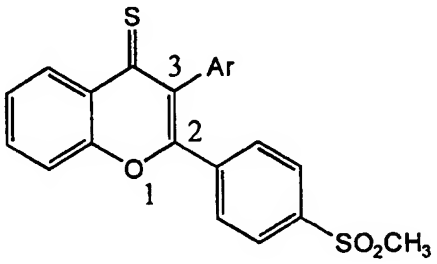
mp: 203～205℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.67～8.64(1H, m), 7.88～7.85(2H, d), 7.80～7.75(1H,m), 7.60～7.57(2H, d), 7.55(1H, s), 7.51～7.46(1H, m), 7.16～7.02(4H, m), 3.06(3H, s)

IR(KBr): 2929, 1605, 1589, 1536, 1508, 1459, 1400, 1377, 1314, 1297, 1254, 1151, 833 cm^{-1}

[Example 37 - 46]

The inventive compounds of Examples 37 - 46 were produced by the same procedure described in Example 36, but substituting appropriate benzopyranone for 3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one. These compounds and their physical properties are shown in Table 2.



<Table 2>

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
37	phenyl	204-206	8.68~8.65(1H,m),7.84~7.81(2H,d), 7.80~7.74(1H,m), 7.60~7.58 (2H,d), 7.55(1H,s),7.50~7.45(1H,m), 7.36~7.34(3H, m), 7.18~7.15(2H,m), 3.04(3H, s)	2931, 1589, 1455, 1375, 1298, 1150
38	2, 3-dichlorophenyl	191-192	8.65~8.63(1H,m),7.91~7.89(2H,m), 7.82~7.76(1H,m),7.67~7.64(2H,m), 7.59~7.56(1H,m),7.52~7.46(2H,m), 7.22~7.16(1H, m), 7.05~7.02(1H,m), 3.06(3H, s)	1594, 1542, 1457, 1296, 1152
39	3-methylphenyl	201-202	8.68~8.64(1H,m),7.85~7.82(2H,m), 7.57~7.54(1H,m),7.49~7.44(1H,m), 7.26~7.16(2H,m), 6.97~ 6.94(2H,m), 3.04(3H,s), 2.30(3H, s)	1607, 1539, 1458, 1374, 1299, 1264, 1152
40	3-chlorophenyl	196-198	8.64~8.61(1H,m),7.88~7.85(2H,m), 7.77~7.74(1H,m),7.61~7.55(3H,m), 7.50~7.45(1H,m),7.34~7.24(2H,m), 7.17~7.16(1H, m), 7.06~7.03(1H,m), 3.05(3H, s)	1589, 1249, 1152
41	2-methylphenyl	234	8.68~8.64(1H,m),7.85~7.82(2H,m), 7.81~7.78(1H,m),7.61~7.58(2H,m), 7.51~7.48(1H, m), 7.33~7.16(4H,m), 7.01~ 6.99(1H, m), 3.04(3H, s), 2.08(3H, s)	2913, 1590, 1541, 1458, 1298, 1253, 1150
42	3, 4-dichlorophenyl	168	8.65~8.60(1H,m),7.93~7.90(2H,m), 7.82~7.76(1H,m), 7.63~7.60 (2H, m), 7.58~7.41(3H, m), 7.28(1H, d), 7.03~6.99(1H, m), 3.07(3H, s)	1591, 1463, 1319, 1243, 1153, 774
43	4-methylphenyl	204-205	8.68~8.64(1H,m),7.84~7.82(2H,d), 7.78~7.73(1H,m),7.61~7.59(2H,d), 7.57~7.44(2H,m),7.17~7.15(2H,d) ,7.05~7.02(2H, d), 3.05(3H, s), 2.37(3H, s)	2918, 1593, 1370, 1298, 1251, 1149
44	4-methoxyphenyl	199	8.68~8.65(1H,d),7.86~7.83(2H,d), 7.78~7.72(1H,m),7.62~7.59(2H,d), 7.56~7.44(2H, m),7.09~7.06(2H,d), 6.89~6.87(2H, d), 3.83(3H, s), 3.05(3H, s)	1590, 1510, 1459, 1297, 1152

Example	3-Ar	mp (℃)	^{1}H NMR($CDCl_3$, 300MHz); δ	IR(KBr) ; cm^{-1}
45	2-fluorophenyl	198- 200	8.67～8.64(1H,d),7.88～7.85(2H,d), 7.80～7.75(1H,m), 7.66～7.63(2H,d), 7.57～7.55(1H,d), 7.50～ 7.45(1H,t), 7.36(1H, m), 7.14～ 7.06(3H, m), 3.05(3H, s)	3088, 1591, 1537, 1465, 1460, 1376, 1152, 757
46	3-fluorophenyl	212	8.65～8.63(1H,m), 7.87～7.85(2H, m), 7.80～7.74(1H, m), 7.63～7.55 (3H, m), 7.50～7.45(1H, m), 7.36 ～7.28(1H, m), 7.08～7.02(1H, m), 6.96～6.89(2H, m), 3.05(3H, s)	3032, 1591, 1297, 1261, 1127

[Example 47] 2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one

Step1:3-Bromo-6-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one

A solution of 6-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one(7.43g, 25.95mmol) from Example 34, Step 2 and NBS(6.93g, 38.93mmol) in $CHCl_3$(100㎖) was refluxed for 20 hours. The resulting mixture was washed with saturated $NaHCO_3$, brine and dried over anhydrous $MgSO_4$. Recrystallization of the resulting residue by CH_2Cl_2 and petroleum ether yielded the title compound as a solid(7.38g, 78%).

mp: 228～229℃

^{1}H NMR($CDCl_3$, 300MHz): δ 7.93(1H. dd, J=7.8, 3.0Hz), 7.84～7.79(2H, m), 7.5～7.50(1H, m), 7.48～7.41(1H, m), 7.39～7.34(2H, m), 2.56(3H, s)

IR(KBr): 1651, 1477, 1261, 1062, 823cm^{-1}

Step 2: 3-Bromo-6-fluoro-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one

To a solution of 3-bromo-6-fluoro-2-(4-(methylthio)phenyl)-4H-1 -

benzopyran-4-one(7.3g, 19.9mmol) from Step 1 in CH_2Cl_2(700㎖) was added a solution of MCPBA(4.0g, 19.9mmol) in CH_2Cl_2(200㎖) at a temperature of 0℃ for 2 hours. The solution was washed two times with saturated Na_2CO_3(100㎖ per each) and the organic layer was washed with H_2O, brine and dried over anhydrous $MgSO_4$. After the solvent being evaporated, the resulting solid was subjected to flash chromatography using a mixture of ethyl acetate : CH_2Cl_2(1 : 1) as an eluant to yield the title compound as a solid(6.1g, 80%) .

mp: 172～174℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.05～8.01(2H, m), 7.96～7.93(1H, m), 7.86～7.82(2H, m), 7.57～7.44(2H, m), 2.83(3H, s)

IR(neat): 2988, 1657, 1481, 1275, 1261, 1081㎝$^{-1}$

Step 3; 2-(4-(Aminosulfonyl)phenyl)-3-bromo-6-fluoro-4H-1-benzopyran -4-one

A solution of 3-bromo-6-fluoro-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one(6.17g, 16.18mmol) in TFAA(trifluoroacetic anhydride, 100㎖) was refluxed for 2 hours. The solvent was removed and the resulting residue was coevaporated three times with using a triethylamine/MeOH solution(50㎖, 1:1) to yield oil. The oil was dissolved in AcOH(100㎖) and treated at room temperature with Cl_2 in AcOH(50㎖). After stirring for 2 hours, the solvent was removed and THF(100㎖) was added to the resulting product. After excessive amount of NH_4OH solution was added at a temperature of 0℃, the reaction mixture was stirred for 2 hours at room temperature. Water was added and the product was extracted two times with ethyl acetate(100㎖ per each). The extract was dried over anhydride $MgSO_4$ and concentrated. Recrystallization of the resulting residue by CH_2Cl_2 and petroleum ether yielded the title compound as a solid(3.83g, 60%).

mp: 266～267℃

^{1}H NMR($CDCl_3$-MeOH-d_4, 300MHz): δ 8.12~8.10(2H, m), 8.02~7.99(2H, m), 7.92(1H, dd, J=8.1, 3.0Hz), 7.64~7.51(2H, m)

IR(KBr): 3300, 3236, 1647, 1552, 1481, 1333, 1163, 1081, 755 cm^{-1}

Step 4 : 2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but substituting benzeneboronic acid(0.056g, 0.459mmol) for 4-fluorobenzeneboronic acid and 2-(4-(aminosulfonyl)phenyl)-3-bromo-6-fluoro-4H-1-benzopyran-4-one(0.153g, 0.38mmol) for 3-iodo-2-(4-(methylsulfonyl)-phenyl)-4H-1-benzopyran-4-one, the title compound was obtained as a solid(0.08g, 53%).

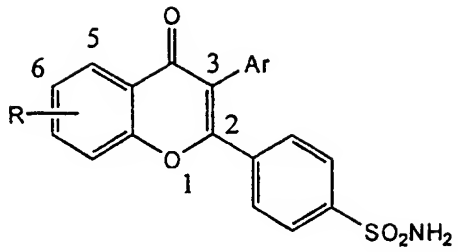
mp: 265~267℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 8.22~8.19(2H, m), 7.96~7.94(2H, m), 7.82 ~ 7.75(1H, m), 7,60(1H, d, J=8.4Hz), 7.54(2H, bs, NH_2), 7.46(1H, m), 7.32~7.19(5H, m)

IR(KBr): 3358, 3268, 3069, 2924, 1691, 1481, 1306, 1164, 750 cm^{-1}

[Example 48 - 58]

The inventive compounds of Examples 48 - 58 were produced by the same procedure described in Example 47, step 4, but substituting appropriate boronic acid or boronate for benzeneboronic acid and in case of Example 52 - 58, the requisite starting material, 2-(4-(aminosulfonyl)phenyl)-3-bromo-4H-1-benzopyran-4-one was prepared in the same way to 6-fluoro analog from 2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one. These compounds and their physical properties are shown in Table 3.



<Table 3>

Example	3-Ar	6-R	mp (℃)	^{1}H NMR(300MHz); δ	IR(KBr) ; cm^{-1}
48	4-fluorophenyl	F	224-226	(DMSO-d_6); 7.93(1H,dd,J=8.1,3.0Hz), 7.88~7.85(2H,m),7.59~7.48(4H,m), 7.20~7.16(2H,m),7.07~7.01(2H,m), 4.86(2H, bs, NH_2)	3408, 3226, 3083, 1631, 1484, 1166, 768
49	4-methylphenyl	F	215-217	($CDCl_3$); 7.91(1H,dd,J=8,1,3.0Hz), 7.84 ~7.81(2H,m),7.58~7.53(3H, m), 7.49~7.45(1H,m), 7.15~7.12 (2H, m), 7.07~7.05(2H, m), 4.99(2H, bs, NH_2)	3240, 3075, 2924, 1629, 1482, 1343, 1185, 729
50	4-chlorophenyl	F	215-217	($CDCl_3$); 7.92(1H,dd,J=8,4,3.0Hz), 7.89~7.85(2H, m), 7.60~7.45(4H,m), 7.34~7.30(2H,m),7.16~7.13(2H, m), 4.93(2H, bs, NH_2)	3386, 1629, 1481, 1343, 1185, 1095, 775
51	3-fluorophenyl	F	257-258	($CDCl_3$);7.92(1H,dd,J=8,1,3.0Hz), 7.61~7.49(4H,m) 7.09~7.02(1H,m), 6.97~6.93 (2H,m), 4.86(2H, bs, NH_2)	3413, 3334, 3229, 1638, 1485, 1335, 1273, 1166, 764
52	4-fluorophenyl	H	267- 268	($CDCl_3$/MeOH-d_4);8.27(1H,dd,J= 8.4,1.8Hz), 7.88~ 7.77(3H,s), 7.62 ~7.48(4H, m), 7.22~7.17 (2H,m), 7.07~7.01(2H,m)	3331, 3219, 1627, 1470, 1338, 1116, 834
53	phenyl	H	218-220	($CDCl_3$/MeOH-d_4); 8.32~ 8.29(1H,m), 7.83 ~7.80(2H,m), 7.75 ~7.71(3H,m), 7.57~7.43 (2H,m), 7.34~7.32(3H,m),7.21~7.18 (2H, m), 4.86(2H, bs, NH_2)	3302, 2929, 1631, 1468, 1344, 1146, 768

Example	3-Ar	6-R	mp (℃)	^{1}H NMR(300MHz); δ	IR(KBr) ; cm^{-1}
54	3, 4-methylenedioxy	H	225-228	(DMSO-d_6);8.14～8.11(1H,m) ,7.90～7.52(7H,m), 7.46(2H,brs), 6.85 ～ 6.82 (2H,m), 6.58(1H,m), 6.03(2H,s)	3387, 2931, 1615, 1486, 1340,1243, 1168,1037, 768
55	4-methoxyphenyl	H	252-254	(DMSO-d_6);8.14～8.11(1H,m), 7.89～7.51(7H, m), 7.45(2H,brs), 7.13～ 7.10 (2H, m), 6.90～6.87(2H, m), 3.75(3H,s)	3315, 3224, 2929, 1600, 1466, 1350, 1238,1150, 768
56	4-methylthiophenyl	H	224-226	(DMSO-d_6); 8.14～8.11(1H,m), 7.92～7.52(7H, m), 7.47(2H,brs), 7.21～ 7.12 (4H, m), 2.50(3H,s)	3333, 2931, 1609, 1467, 1353, 1168, 730
57	3,4-dichlorophenyl	H	215-217	(DMSO-d_6); 8.16～8.12(1H,m), 7.94～7.40(4H, m), 7.68～7.64(2H, m), 7.60～7.54(3H, m),7.16～7.12 (1H, m), 7.47(2H,brs)	3302, 2929, 1631, 1468, 1344, 1146, 768
58	2-fluorophenyl	H	215-217	(DMSO-d_6); 8.15～8.11(1H,m), 7.92 ～7.88(1H, m), 7.81～7.55(6H, m) ,7.48(2H,brs), 7.42～7.36(1H, m), 7.27～7.14 (3H, m)	3317, 3203, 1615, 1432, 1320, 1113, 760

[Example 59] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

Step 1; 7-Fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 1, Step 5, but replacing 3-iodo-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one by of 3-bromo-7-fluoro-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one(0.3g, 0.79mmol) prepared from 7-fluoro-2-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one in an analogous way to 6-fluoro analog of Step 1, and Step 2 in Example 47 , the title compound was obtained(0.26g, 82%).

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33~8.30(1H, m), 7.70~7.63(2H, m), 7.50~7.43(2H, m), 7.61(1H, brs), 7.28~7.25(1H, m), 7.23~7.16(2H, m), 7.05~6.99(2H, m), 2.73(3H, s)

Step 2: 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

Following the procedure of Example 47, Step 3, but substituting 7-fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one(0.18g, 0.454mmol)for3-bromo-6-fluoro-2-(4-(methyl-sulfinyl)phenyl)-4H-1-benzopyran-4-one, the title compound was obtained as a solid(0.07g, 37%).

mp: 214~215℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.34~8.29(1H, m), 7.88~7.85(2H, m), 7.55~7.52(2H, m), 7.25~7.15(4H, m), 7.07~7.01(2H, m), 4.94(2H, s)

[Example 60] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 7-fluoro-3-(2-fluorophenyl) -2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 59, Step 2.

mp: 188℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.34~8.29(1H, m), 7.87~7.85(2H, m), 7.59~7.56(2H, m), 7.40~7.32(1H, m), 7.25~7.02(5H, m), 4.96(2H, s)

[Example 61] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 7-fluoro-3-(3-fluorophenyl) -2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one according to the procedure

described in Example 59, Step 2.

mp: 239~240℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 8.26~8.21(1H, m), 7.85~7.82(2H, m), 7.58~7.55(2H, m), 7.47~7.44(1H, m), 7.38(2H, s), 7.36~7.28(2H, m), 7.11~6.97(3H, m)

[Example 62] 2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 7-fluoro -3-(3,4-dichlorophenyl) -2-(4-(methylsulfinyl)phenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 59, Step 2.

mp: 190~191℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.33~8.28(1H, m), 7.91~7.89(2H, m), 7.57~7.54(2H, m), 7.41~7.37(2H, m), 7.23~7.19(2H, m), 7.00~6.97(1H, m), 4.98(2H, s)

[Example 63] 2-(4-Aminosulfonyl)phenyl-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-aminosulfonyl)phenyl-3-bromo -6-methoxy-4H-1-benzopyran-4-one according to the procedure described in Example 47, Step 4.

^{1}H NMR($CDCl_3$, 300MHz): δ 7.87(2H, m), 7.54~7.53(2H, m),7.51~7.37(2H, m),7.22~7.00(5H, m), 4.90(2H, s), 4.01(3H, s)

[Example 64] 2-(4-(Aminosulfonyl)phenyl)-7-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-(aminosulfonyl) -phenyl)-3-

bromo-7-methoxy-4H-1-benzopyran-4-one according to the procedure described in Example 47, Step 4.

mp: 245℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.21~8.18(1H, m), 7.87~7.85(2H, m), 7.62~7.60(2H, m),7.22~7.05(6H, m),4.87(2H, s), 4.09(3H, s)

[Example 65] 2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl) -5-methoxy-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl) -3-bromo-8-chloro-5-methoxy-4H-1-benzopyran-4-one according to the procedure described in Example 47, Step 4.

mp: 279~281℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 7.96(1H, dd, J=9.0, 1.2Hz), 7.79~7.76(2H, m), 7.59~7.42(3H, m), 7.46(2H, bs, NH2), 7.25~7.14(4H, m), 3.84(3H, s)

IR(KBr): 3290, 3220, 1627, 1467, 1416, 1320, 1226, 1162, 1037, 815 cm^{-1}

[Example66]2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-hydroxy-4H-1-benzopyran-4-one

To a solution of 2-(4-(aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-methoxy-4H-1-benzopyran-4-one(0.03g, 0.07mmol) in CH_2Cl_2(5㎖) was added 1.0M BBr_3(0.2㎖) at a temperature of 0℃. The mixture was stirred for 4 hours at room temperature and diluted with CH_2Cl_2(10㎖). After being washed with water and brine, the solution was dried over anhydrous $MgSO_4$. The crude product was purified by flash chromatography to yield the title compound as a solid(0.02g, 74%).

mp: 251~252℃

^{1}H NMR(DMSO-d_6, 300MHz): δ 7.93(1H, d, J=9.3Hz), 7.81~7.78(2H, m), 7.62~7.60(2H, m), 7.48(2H, bs, NH_2), 7.32~7.18(5H, m)

IR(KBr): 3311, 3234, 1639,, 1592, 1434, 1223, 1167, 712cm^{-1}

[Example67]2-(4-(Aminosulfonyl)phenyl)-6-hydroxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl)-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 66.

^{1}H NMR($CDCl_3$, 300MHz): δ 7.88~7.84(2H, m), 7.73~7.70(2H, m),7.60~7.51(3H, m),7.45(1H, s),7.21~7.16(2H, m),7.09~7.02(2H, m), 4.92(2H, s)

[Example 68] 2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl) -6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 36.

mp: 224~225℃

^{1}H NMR($CDCl_3$, 300MHz): δ 8.32(1H, dd, J=8,4, 3.0Hz), 7.85~7.82(2H, m), 7.82~7.47(4H, m), 7.15~7.11(2H, m), 7.08~7.02(2H, m), 5.30(2H, bs, NH_2)

IR(KBr): 3370, 3278, 1597, 1493, 1342, 1258, 1159, 1086, 768cm^{-1}

[Example 69] 2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione

The title compound was prepared from 2-(4-(aminosulfonyl)phenyl) -3-(4-fluorophenyl)-4H-1-benzopyran-4-one according to the procedure described in Example 36.

mp: 197~199℃

^{1}H NMR($CDCl_3$-MeOH-d_4, 300MHz): δ 8.67~8.63(1H, m), 7.84~7.75(3H, m), 7.59~7.46(5H, m), 7.16~7.12(2H, m), 7.06~7.01(2H, m)

IR(KBr): 3265, 1590, 1536, 1339, 1250, 1154, 1069, 832 cm^{-1}

[Experimental example 1]

Regarding the compounds in the above Examples and indomethacin, the inhibition efficacy of COX-2 and COX-1 are being measured by the following two methods. And the results of the inhibition efficacy of COX-2 and COX-1 are shown in Table 4.

1. Evaluation of COX-2's inhibition efficacy(J. Pharmacol.Exp.Ther.166,96(1969))

After cleaning C57BL/6 mouse's abdomen by 70% EtOH, the skin of mouse's abdomen was eliminated cautiously not to harm peritomeum and 5㎖ of cold PBS was poured into the abdominal cavity and in certain times later macrophage-bleeding abdominal-liquid was collected by syringe. By adding RPMI-1640 badge containing penicillin(100unit/㎖) and streptomycin(100 mg/㎖) to cell pellet obtained by centrifugation of collected liquid about 5 minutes in 1500 rpm, it was disperesed and also COX-1 existing in the cell was inactivated by treating with 500 μM aspirin. After putting 1㎖ cell suspension having cell number of 1×10^6cells/㎖ into each 24-well microtiter plates, macrophages were adhered to the bottom of plate by culturing in the condition of 5% CO_2/95% O_2, at a temperature of 37℃ for 2 hours. Other cells not being adhered to were eliminated by washing two times with PBS. The purity of macrophages obtained through this process was identified by differential counting. After adding RPMI-1640 badge(normally 5×10^5 cell/㎖) containing 3% right fetal blood serum to macrophage and treating it with LPS(lipopolysaccharide) to make final

concentration as 10㎍/㎖, it was cultured in the condition of 5% CO_2, at a temperature of 37℃ for 16 hours. After inducing COX-2 by LPS, the cell culture medium was eliminated and macrophages was washed two times with PBS. And 1㎖ of RRPI-1640 badge was added to each well again and after treating them with sample with appropriate concentration, they were cultured at a temperature of 37¡É for 10 minutes. And then treated them with arachidonic acid to make their final concentration as 10 μM and cultured them additional 10 minutes, all the supernatant liquid of reaction was obtained. The amount of PGE_2 produced in the supernatant liquid of reaction was determined by the PGE_2 radioimmuno assay. The 100% COX-2's activation is referenced by the difference of the amount of PGE_2 produced in the supernatant liquid of reaction between with 10 μM arachidonic acid treatment and without 10 μM arachidonic acid treatment.

2. Evaluation of COX-1's inhibition efficacy

Following the same procedure as the above evaluation of COX-2's inhibition efficacy, but there is no pre-treatment of aspirin and LPS in the adhesion of macrophage.

<Table 4>

Example	Inhibition(%)					Example	Inhibition(%)				
	COX-2 (μg/mℓ)			COX-1 (μg/mℓ)			COX-2 (μg/mℓ)			COX-1 (μg/mℓ)	
	10	1	0.1	10	1		10	1	0.1	10	1
1		100	94	<5		39	86	31	11		
2	81	68	34	<5		40	69	29	6	<5	
3	72	61	13			41	96	36	<5	<5	
4	5<			<5		46	91	67	4		
5	100	90	39			47		86	23		
6	100	92	42			48		100	63	48	36
9	29	5<		<5		49	92	76	32		
10	86	67	14	<5		50	87	80	5		
11		89	46	<5		51	100	83	56	6	
14	71	32	18			52	99	96	73	67	62
15	90	83		13		53	92	90	76	61	52
16	24			<5		54		84	20	75	
17	13			<5		55	100	90		84	66
18	86	51		18		56	90	84	53	90	77
19	35	18		11		57		96	48	75	
20	85	<5		<5		58	96	63		60	34
21	55	35		<5		59		100	39		
22	90	82	14			60		100	43		
23	97	84	23			61		97	69	38	22
24	95	86	22			62		100	89	76	54
33	44	27		17		64	47	52	<5		
34	78	66		12		65	93	67		73	24
36	100	80	56	<5		66	90	83		80	40
37	88	76	47	<5		68		100	89	83	58
38	96	77	18			69	100	98	42	90	68

[Experimental example 2]

Regarding the compounds in some of the above Examples and indomethacin, depressant action on edema in mouse's ear and depressant action on edema in mouse's foot being induced by carrageenan are being measured by the following 2 methods. And the results of the depressant action on edema in mouse's ear and depressant action on edema in mouse's foot being induced by carrageenan

are shown in Table 5.

1. Measurement of depressant action on edama in mouse's ear

At 30 minutes after coating the left ear of ICR mouse, weighing 20g, with a solution of appropriate amount of sample in 20㎕ of mixed solvent DMSO : acetone(1:9), 25 ㎍ of TPA(tetradecanoylphorbol acetate) was coated on both ears. The determination of depressant action on edama was made in 5 hours later by the number of neutral granulocyte gathering in the ear after inducing TPA inflammation. The number of neutral granulocyte was estimated by measuring the activation of myeloperoxidase.

2. Measurement of depressant action on edama in mouse's foot induced by carrageenan

At 1 hour after oral administering to Male-Sprague-Dawley-white mouse, weighing 150 ~ 200 g, with a suspended solution of appropriate amount of sample in 0.5% of carboxymethyl cellulose and 0.2% of TWEN solution, edema on the right foot of mouse was induced by injecting 0.1㎖(1%) of carrageenan-saline solution. Right after the inducement of edema by carrageenan and 3 hours later, the edema rate was estimated by measuring white mouse's foot volume with Displacement Plethysmometer(Ugo Basile, Italy). Carrageenan injection Drug was administered 1 hour before the carrageenan injection. Depressant rate of edema is produced by the following equation 1.

[Equation 1]

% Depressant rate of edema =

$$(1-\Delta V_{\text{treated group}}/\Delta V_{\text{control group}}) \times 100$$

ΔV : change of foot volume

<Table 5>

	depressant rate of ear edema (ED50, % depressant rate)	depressant rate of edema rate induced by carrageenan(oral administration) (ED50, % depressant rate)
indomethacine	0.4 mg/ear, ED50	4.3 mg/kg, ED50 p.o.
Example 1	0.4 mg/ear, ED50	50mg/kg, 43% depression
Example 2	-	-
Example 3	1.2 mg/ear, ED50	50mg/kg, 52% depression
Example 5	-	-
Example 6	-	50mg/kg, 37% depression
Example 10	0.6 mg/ear, ED50	-
Example 11	-	30mg/kg, 17% depression
Example 12	0.4 mg/ear, ED50	30mg/kg, 20% depression
Example 14	-	-
Example 15		30mg/kg, 41% depression
Example 26	0.6 mg/ear, ED50	50mg/kg, 23% depression
Example 27	-	-
Example 28	0.8 mg/ear, ED50	-
Example 34		3mg/kg, 23% depression
Example 36	1.0 mg/ear, ED50	30mg/kg, 20% depression
Example 37		30mg/kg, 16% depression

As can be seen from the above Table 4, the compound(I) of the present invention has high selectivity on COX-2 so that it could inhibit the action of COX-2.

The present invention relates to the cyclooxygenase-2 inhibitor composition having one or more of which is selected from non-toxic, pharmaceutically acceptable carrier or adjuvant or diluent or other activating components with pharmaceutically effective amount of compound(I), and the composition of the present invention may be oil or could be in the form of solution, suspension or emulsion in aqueous medium or could be in the form of powder that is melted in sterile and pyrogen-free water before being used as oral formulation or parenteral formulation such as hypodermic injection, vein injection, intramuscular injection,

sternal injection, suppository or cream or gel or ointments or local formulation such as suspension, mouth washing.

In case of oral formulation, the composition of the present invention is prepared by the disclosed method of employing pharmaceutically acceptable carrier and excipient, for example, in the form of tablet, troches, saccharated tablet, aqueous or oily suspension, dispersive powder or particle, emulsion, soft or hard capsule, syrup, elixir, and it's stored by unit dosage or in multicapacity container.

The tablet, one of oral formulation, has the compound of the present invention mixed inactive additives which could be used in the preparation of tablet. The example may include, but not limited to, excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, sodium phosphate or pelletizing agents such as corn, starch, alginic acid or disintegrating agents or coupling agents such as starch, gelatin, acacia or lubricants such as magnesium stearate, stearic acid, talc. The tablet is used without coating, or is used with coating to prevent absorption in gastrointestinal and disintegration of tablet. For example, time inhibitors such as glyceryl-mono-stearate or glyceryl-di-stearate is applicable. Hard capsule is a mixture of the compound of the present invention with solid diluent such as calcium carbonate, calcium phosphate, kaolin, and soft capsule is a mixture of the compound of the present invention with active components, which are mixtures of solvents such as water, mixable polyethyleneglycol, PEGs, ethanol with oil solvents such as peanut oil, liquid paraffin, olive oil.

Liquid suspensions is a mixture of active components with excipients, which is appropriate for preparation of liquid suspension. Excipinet for liquid suspensions is, for example, suspensions such as sodium carboxymethyl cellulose, methyl cellulose, hydroxy-propylmethyl cellulose, sodium alginic acid, polyvinyl-pyrrolidone, gum tragacanth, gum acacia or polyoxylenestearate which is a condensate of fatty acid and alkylene oxide or heptadecaethyleneoxycetanol which

is a condensate of long fatty acid and alkylene oxide; polyoxyethylenesorbitolmonoolate which is a condensate of hexitol anhydride and ester derived from fatty acid and ethylene oxide or humectants or dispersing agents. Liquid suspensions may further contain preservatives, colorants, condiments, sweeteners.

Oil suspensions is a mixture of vegetable oil such as olive oil, sesami oil or mineral oil such as liquid paraffin with active components, for example, it contains thickening agents such as beeswax, soft paraffin, cetyl alcohol. Also it contains preservatives, colorants, condiments, sweeteners, but such composition may contain antioxidants such as vitamin-c to improve shelf life.

Dispersive powder or particle contains active component in a mixture of dispersing agents, humectants, suspending agents and preservatives. The example of an adequate dispersing agent is humectants and suspending agents which are mentioned above. Additional excipient, for example, is sweeteners, condiments, colorants and etc.

Water in oil emulsion is a mixture of oil phase like vegetable oil such as olive oil or mineral oil such as liquid paraffin with emulsifier like natural phospholipid such as soy bean lecithin or sorbitanmonoolate, which is derived from hexitol anhydride or fatty acid ester, or reoxyethylenesorbitolmonoolate which is a condensate of hexitol anhydride and ester derived from fatty acid and ethylene oxide.

Syrup and elixir is a mixture of sweetener such as glycerol, propyleneglycol, sorbitol, sucrose with active components.

Parenteral formulation is injected in the form of suspension which is a mixture of sterile injectable solution or non-toxic, pharmaceutically acceptable diluting agents or solvents sucha as 1,3-butane-diol with active component. Available excipient or solvents is, for example, water, Ringer's solution and

isotonic sodium chloride solution. Cosolvent such as ethanol, polyethyleneglycol, polyprolyleneglycol is also available. Also, bland fixed oil could be commonly used as a solvent or a suspending solvent. And bland fixed oil for this purpose is used with synthetic mono-, di- glyceride. Also, fatty acid like oleic acid could be used in the preparation of injection. Suppository form is prepared by mixing with appropriate bland excipients such as cocoa butter and polyethyleneglycol, which keep suppository as solid form at room temperature and make suppository melt inside rectum. It is administered through rectum.

Local formulation generally consists of pharmaceutical carrier, auxiliary solvent, emulsifier, penetration accelerant, preservative and palliative.

In case of treating diseases with composition of the present invention, the dosage of active component of compound(I) depends on the patient's age, weight, general health condition, sex, meal, administration time, evacuation speed, drug combination, and severity of disease during treatment, but it could be used in the range of 0.01～140mg per 1kg(weight) per day according to the kind of diseases, or 0.5mg～7g per patient. For example, inflammation could be effectively treated with administering 0.01～50mg per 1kg(weight) or 0.5mg～3.5g per patient.

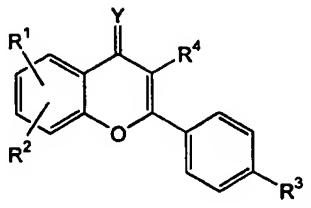
On the one hand, the amount of the compound of the present invention which would be mixed with carrier material to decide one formulation is different according to the way of administration paths and treating patients. For example, in formulation for oral administration to human, it consists of 5 ~ 95% of carrier materials and 0.5mg～5g of active components and in formulation for parenteral administration to human, it consists of 5～99% of carrier materials and 0.1mg～2.5g of active components in the oral administration.

It is understood that the foregoing detailed description is given merely by way of illustration and that modifications and variations may be therein without departing from the spirit and scope of the invention.

CLAIMS

1. A compound represented by the following general formula(I) :

(I)



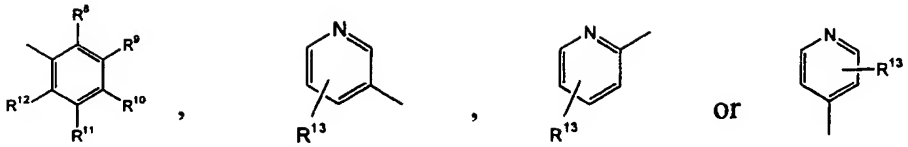
wherein

Y is an oxygen atom or a sulfur atom;

R^1 and R^2, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a trifluromethyl group, an alkoxy group, a hydroxy group, a nitro group, a nitrile group, or a carboxyl group;

R^3 is a group of a formula : $S(O)nR^5$ wherein n is an integer of $0 \sim 2$, R^5 is a hydrogen atom, a C_1 -C_6 lower alkyl group, or a group of a formula : NR^6R^7 wherein R^6 and R^7, identical to or different from each other, are independently a hydrogen atom, or a C_1 -C_6 lower alkyl group; and

R^4 is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, benzodioxolyl, or a substituted group presented by the following structures :



wherein

R^8 through R^{12}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 - C_6 lower alkyl group, a triflurometh yl group, an alkoxy group, a hydroxy group, a hydroxyalkyl group, a nitro group, a group of a formula : S(O)nR^5, a group of a formula : NR^6 R^7 , a triflurometh oxy group, a nitrile group, a carboxyl group, an acetyl group, or a formyl group wherein n, R^5, R^6 and R^7 have the same meaning as defined X and R^3 above; and

R^{13} is a hydrogen atom, a halogen atom, a C_1 -C_6 lower alkyl group, a triflurometh yl group, a alkoxy group, a hydroxy group, a triflurometh oxy group, a carboxyl group, or an acetyl group;

or their pharmaceutically acceptable salts.

2. The compound (I) according to claim 1. which is

2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-(methylthio)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-(N,N-Dimethylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-(N-Methylamino)phenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethoxyphenyl)-4H-1-benzopyran-4-

one,

3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Isopropylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Ethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Hydroxymethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-one,

3-(4-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,3-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3,5-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Hydroxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Acetylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,4-Dimethylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Formylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Carboxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Chloro-3-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-5-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Fluorophenyl)-5-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-

one,

3-(3,5-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(N-methyl-3-pyrazolyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

6-Chloro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,

2-(4-(methylsulfonyl)phenyl)-3-(3-nitrophenyl)-4H-1-benzopyran-4-one,

3-(3,4-Difluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(methylsulfonyl)phenyl)-3-(1-naphthyl)-4H-1-benzopyran-4-one,

3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(4-Bromophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-oxazolyl)-4H-1-benzopyran-4-one,

6-Fluoro-2-(4-fluorophenyl)-3-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Benzo[b]thienyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

3-(2-Chloro-5-pyridinyl)-7-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Methylsulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
7-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(1,3-Benzodioxol-5-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-thiazolyl)-4H-1-benzopyran-4-one,
3-(Benzofuran-2-yl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-pyrazinyl)-4H-1-benzopyran-4-one,
3-(2-Methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-Fluoro-3-(2-methyl-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-Fluoro-3-(2-methoxy-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-5-pyridinyl)-6-fluoro-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
6-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
7-fluoro-3-(2-fluoro-5-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methoxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-(2-trifluoromethyl-5-pyridinyl)-4H-1-benzopyran-4-one,

3-(2-Fluoro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Chloro-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Bromo-3-pyridinyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(2-Furyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(5-Indanyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-one,
3-(4-Fluorophenyl)-6-methyl-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
3-(4-Fluorophenyl)-6-hydroxy-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chloro-3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chloro-4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-((4-methylthio)phenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-((3,4-methylenedioxy)phenyl)-4H-1-benzopyran-4 -one,
2-(4-(Aminosulfonyl)phenyl)-3-(2,3-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2,4-difluorophenyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(3-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxyphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(4-methoxyphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-methoxyphenyl)-4H-1-benzopyran-4-one,.
2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-7-fluoro-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3,5-difluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-chloro-5-pyridinyl)-6-fluoro-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluoro-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methyl-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(2-methoxy-5-pyridinyl)-4H-1-benzopyran-4-one,

2-(4-(Aminosulfonyl)phenyl)-3-(4-pyridinyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-thienyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-3-(2-furyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-phenyl-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-methylphenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-chlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(2-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3,4-dichlorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-hydroxy-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-8-chloro-3-(4-fluorophenyl)-5-methoxy-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-7-methoxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Aminosulfonyl)phenyl)-6-hydroxy-3-(4-fluorophenyl)-4H-1-benzopyran-4-one,
2-(4-(Methylsulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,
3-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-3-(4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -thione,

3-(2-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

7-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(3-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methylphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

6-Fluoro-2-(4-(methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

3-(2-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(2,3-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3,4-Dichlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(4-Chlorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

3-(3-Methoxyphenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4-thione,

2-(4-(Methylsulfonyl)phenyl)-3-(4-trifluoromethylphenyl)-4H-1-benzopyran-4-thione,

3-(3-Chloro-4-fluorophenyl)-2-(4-(methylsulfonyl)phenyl)-4H-1-benzopyran-4 -thione,

2-(4-(Methylsulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(3-pyridinyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(2-fluorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-(4-chlorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-3-phenyl-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-6-fluoro-3-(4-fluorophenyl)-4H-1-benzopyran-4-thione,

2-(4-(Aminosulfonyl)phenyl)-7-fluoro-3-(3-pyridinyl)-4H-1-benzopyran-4-thione

3. A cyclooxygenase-2 inhibitor composition comprising:

an effective amount of a compound according to claim 1 and a pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00469

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C 07 D 311/30, 405/04, 413/04, 407/04, 409/04, 417/04; A 61 K 31/352, 31/4433

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C 07 D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem.Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, STN: CA, EPO: WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Chemical Abstracts, Vol.68, No.19, 06 May 1968 (Columbus, Ohio, USA), page 8393, column 2, abstract No.87102k, G.Srimannarayana et al.:"Synthesis of 3-substituted flavones as potential insecticides", Symp.Syn.Heterocycl.Compounds Physiol.Interest, Hyderabad, India, 1964, 58-63 (1966).	1
A	Chemical Abstracts, Vol.88, No.15, 10 April 1978 (10.04.78) (Columbus, Ohio, USA), page 546, column 1, abstract No.105064u, K.L.Prasunamba et al.:"Photochemical cyclization of 2,3-diarylchromones: formation of phenanthro(9'10':2,3)chromones", Indian J.Chem.Sect.B, 756-8 (1977).	1
A	Chemical Abstracts, Vol.109, No.17, 24 October 1988 (24.10.88) (Columbus, Ohio,USA), page 693, column 2, abstract No.149127y, B.C.B.Bezuidenhoudt et al.:"Oligomeric isoflavonoids. Part 1. Structure and synthesis of the first (2,3')-isoflavone-isoflavane dimer", J.Chem.Soc., Perkin Trans 1, 1227-35 (1988).	1,2

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 1999 (23.09.99)	04 October 1999 (04.10.99)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/200	Hammer Telephone No. 1/53424/374

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00469

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	The Patent Office Japanese Government PAJ CD-Rom 10[021], 31 October 1996 (31.10.96), Patent Abstracts of Japan unexamined Application, Publication number 08-157 361 (TOYAMA CHEM. CO., LTD.)	1,3
A	US 3 844 792 A (ZWEIG), 29 October 1974 (29.10.74).	1
A	WO 96/13 500 A (MERCK FROSST CANADA), 09 May 1996 (09.05.96), claims 4,8.	1,3
A	WO 96/06 840 A (MERCK FROSST CANADA), 07 March 1996 (07.03.96), cited in the application.	1,3

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 99/00469

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
US A 3844792	29-10-1974	keine - none - rien	
WO A 9613500		keine - none - rien	
WO A 9606840		keine - none - rien	